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Nuclear particles in cancer treatment : brief review

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Abstract : Nuclear particle application in cancer treatment has a long history. Physicists played an important role in the development of particle therapy. Experimentations using neutrons, protons, heavy ions and π^- mesons for their therapeutic applications got initiated soon after they are made available.

In the late 30's in Berkeley, California, work began on neutrons, the first particle used for cancer treatment. More than 10,000 patients have been treated with neutrons in about 20 centers around the world. Fast neutrons appear to be the treatment of choice for inoperable salivary gland tumors. The other tumor types or sites for which neutron therapy may benefit are slowly growing, well-differentiated soft tissue sarcomas, melanomas and locally extended prostatic adenocarcinomas.

The use of protons in radiotherapy was proposed in 1946. Biomedical research using protons began in Berkeley, soon after the 184" cyclotron was in operation, but most of the developments and clinical work took place in Uppsala (Sweden), Harvard (USA), USSR and Japan. More than 5000 patients have been treated. Protons appear to be the treatment of choice for choroidal melanoma, and they give impressive clinical results for the treatment of bony and cartilagenous tumors of the skull base and cervical spine. In addition, proton beams are successfully used for pituitary related problems and for the treatment of arterio-venous malformations.

The clinical results with helium ions in Berkeley are very similar to the proton results. Heavy ions, carbon, neon, silicon and argon are also under investigation in Berkeley. About 300 patients have been treated. Although no definitive statements can be made at this time regarding the role of heavy ions in radiotherapy, the results suggest that they may be of value in treating tumors of unusual histology located in sites close to critical structures.

The pion therapy program got started in Los Alamos in 1973 and soon after in Vancouver, Canada and Villigen, Switzerland. Among these three centers, about 1000 patients were treated. The pion therapy program in Los Alamos was discontinued several years ago, but the programs in Vancouver, and Villigen are still in progress. Pion treatment results of glioblastoma patients in Vancouver and nonresectable soft tissue sarcoma patients in Villigen look promising.

The use of charged particles in radiotherapy necessitated the developments of precise treatment planning in three dimensions. The CT and NMR imaging techniques has made it possible to use these beams effectively. In addition to the demonstrated improvements in the treatment of certain tumors, the introduction of nuclear particles in cancer treatment accelerated the overall developments of treatment planning and the radiobiological understanding of acute and late effects in normal tissues. These developments in turn are helping conventional radiotherapy.

Keywords : Nuclear particles, radiotherapy, accelerators.

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1. Introduction

The discipline of Radiotherapy is an excellent example of a successful interdisciplinary effort where physicists play an important role. Of all modalities used

in cancer management, radiation therapy offers the greatest probability of tumor control while preserving normal tissues. Radiotherapy, like surgery, is essentially intended to control local regional cancer. Despite the use of megavoltage X-rays in conventional radiotherapy, approximately 1/3 of the patients treated in the United States die because of failure to control the primary tumor. The rationale of using nuclear particles is to further improve the control of the primary tumor.

Figure 1 shows the schematic representation of target volume and treatment volume as practiced in radiotherapy. The use of high energy X-rays in radiotherapy and increasing knowledge on the nature and extension of tumor helps reduce the

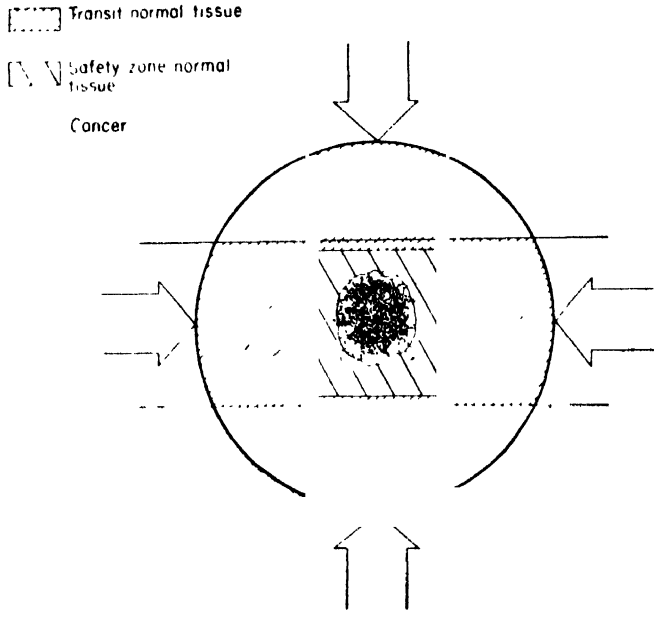

Figure 1. Schematic representation target volume and treatment volume as practiced in radiotherapy.

treatment volume. The treatment volumes in megavoltage radiotherapy, in general, are much larger than the target volumes by a factor of 3 to 6. Surgery currently achieves high control rates for many tumors treated at an early stage and the surgical treatment volumes are very close to the target volumes. The ability to spare the integrity and the function of normal tissues within the treatment volume is what makes radiotherapy preferable to surgery. The therapist gives the maximum dose tolerated by these normal tissues to improve the chances of tumor control. The tolerance of normal tissue decreases with increasing volume of the normal tissue in the radiation field. With the use of heavy charged particles, it is possible to reduce the treatment volume and, hence, increase the dose to the tumor by 10-30% without exceeding normal tissue tolerance.

2. Fractionation in radiotherapy

Early radiation therapy consisted of single treatments. While such treatments were found to be effective for skin cancer, they were not effective for deep seated tumors. As early as 1914, Schwarz suggested that fractionated treatments would be more effective because he felt that the mitotic cells may be more radiosensitive. However, the rationale for fractionation came from the famous experiments in 1927 on the ram testicle. The skin of the testicle as a model for normal tissue and the sterilization of the testicle as a model for tumor sterilization were considered. It was shown that by fractionating the total dose, sterilization can be achieved with less skin damage. Another newly recognized rationale for fractionation could be the presence of hypoxic but viable tumor cells that are radioresistant. During fractionation, the hypoxic cells get reoxygenated making them radiosensitive. The redistribution of tumor cells in cell cycle and reoxygenation of hypoxic tumor cells during fractionation sensitize tumor cells. We can say that the tumor cells sensitize themselves during fractionated treatments. With the introduction of megavoltage X-rays, the limiting normal tissues are generally non-proliferating and hence will not be sensitized. The introduction of particles in radiotherapy stimulated radiobiological investigations on acute and late effects of normal tissues and their modification with LET. Now it is further established that at a dose of $\sim$ 2Gy/fr, the late responding normal tissues are spared preferentially compared to acutely responding normal tissues.

3. Rationale of using nuclear particles in radiotherapy

The use of nuclear particles in radiotherapy is to further improve local tumor control without exceeding normal tissue tolerance.

This can, in principle, be achieved in two ways :

(i) Physical : Use of heavy charged particles with improved dose localization characteristics permit the deliverence of higher tumor doses without exceeding the normal tissue tolerance.

(ii) Radiobiological : Particles may preferentially be more effective on cancer cells compared to normal cells.

3.1. Dose localization characteristics of particles :

Radiations can be broadly divided into two groups : 1. exponentially attenuating and 2. Bragg ionization characteristics with a well defined range. X-rays and fast neutrons belong to the first group and heavy charged particles (protons, heavy ions and pions) belong to the second group. Except for the initial dose build up for high energy X-rays and fast neutrons, the dose decreases with depth of penetration. For heavy charged particles, on the other hand, the dose deposited increases slowly with depth and then rises sharply near the end of the range due to a' Bragg peak effect. There is practically no dose beyond the range of

the particle. Figure 2 shows the depth dose distribution of protons as a representative of heavy charged particles. In addition to the Bragg peak effect near

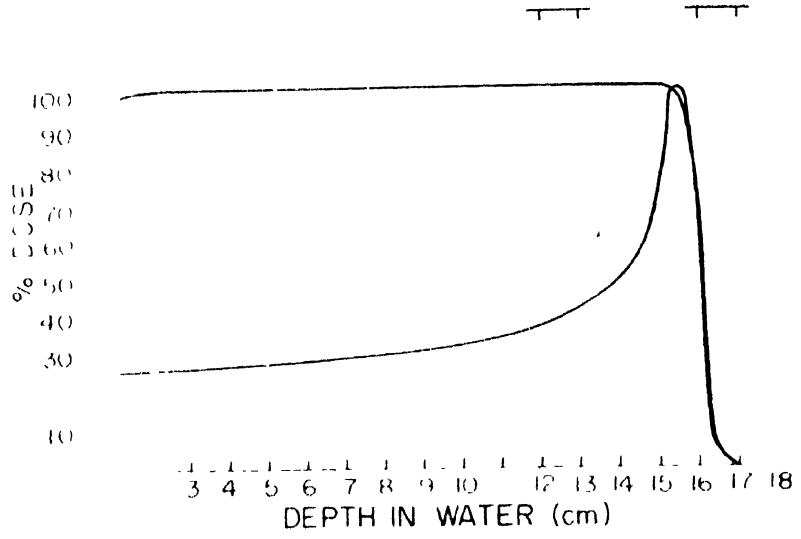

Figure 2. Depth dose distributions of proton beams. Narrow peak is for monoenergetic beam and broad peak is an extreme case of radiating tissue thought out the depth of penetration.

the end of the range, negative pions exhibit a unique phenomenon when they come to rest. Negative pions (being negatively charged) are captured by atomic nuclei in the medium, and the resulting nucleus disintegrates yielding various particles including some short-range and heavily ionizing fragments. In addition to Bragg peak effect, this phenomenon increases the dose with depth. The LET (dE/dx) at the pion stopping region is also increased because of heavily ionizing fragments. The Bragg peak of nearly monoenergetic heavy charged particles extracted from accelerators is quite narrow and is frequently insufficient to cover the treatment volumes encountered in radiotherapy. The Bragg peak can be broadened by introducing an absorber of variable thickness. The dose at the Bragg peak decreases with increasing peak width but is never lower than the dose at the entrance. The linear energy transfer (LET) of heavy charged particles at depth, especially at the Bragg peak position, is greater than at the entrance, whereas for high energy gamma rays and fast neutrons, there are no significant differences in LET with depth of penetration.

X-rays and electrons are often referred to as low-LET radiations, but even these radiations deposit a small fraction of their dose at LET about 30 keV/μm. The high LET component extends to about 100 keV/μm for proton beams, to about 250 keV/μm for helium ion beams, to about 900 keV/μm for pions and fast neutrons, and is even higher for heavy ions. The difference between high-LET

radiations is in relative proportion of does in various LET intervals and the maximum LET. All high-LET radiations are really mixtures of various LET's.

The depth dose distribution of all particles is shown in Figure 3. The depth dose distributions of all charged particles are similar. Among the charged

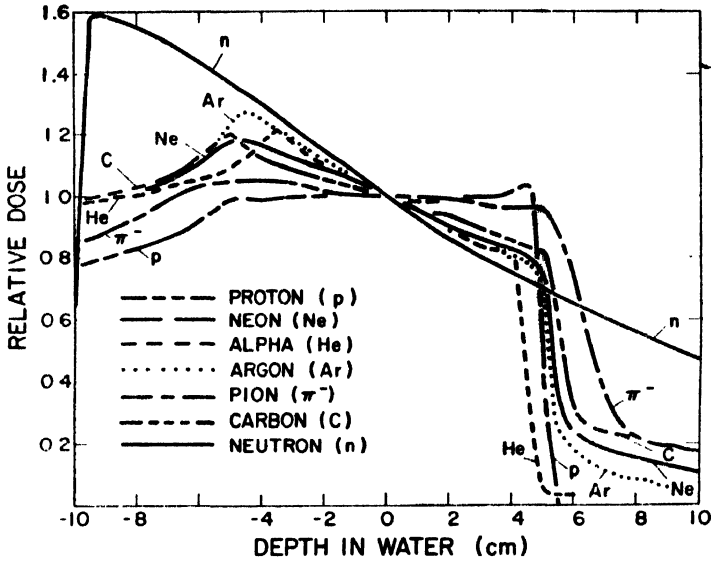

Figure 3. Depth dose distribution of particle.

particles beams, the proton beams are the least expensive to produce and they have the best dose localization advantage. Protons, however, can be considered as a low LET radiation.

3.2. Radiobiological characteristics of particles :

The known major radiobiological factors which affect tumor control include recovery from sublethal and potentially lethal damage, oxygen effect, variation of radiosensitivity as a function of cell cycle (cell age) and cell proliferation after irradiation. The RBE and OER change with LET. The RBE increases with LET reaching a maximum around 100 keV/μm and decreases with further increase in LET due to saturation at higher LET values. The OER decreases with increasing LET reaching unity at around 100 keV/μm (see Figure 4). For therapeutically relevant beams of particles, the typical RBE and OER values are given in Table 1. The repair capacity of cells reduces with increasing LET and, hence, the RBE of high-LET radiations increases with decreasing dose per fraction.

The higher RBE values, by themselves, are of no advantage in radiotherapy unless these values are higher than the RBE values of limiting normal tissues. The RBE of neutrons was found to depend on growth rate of the tumors. The slower the tumor growth rate, the higher the RBE. An RBE value of nearly a

factor of two greater than normal tissues was found for well differentiated lung metastasis from salivary gland tumors.

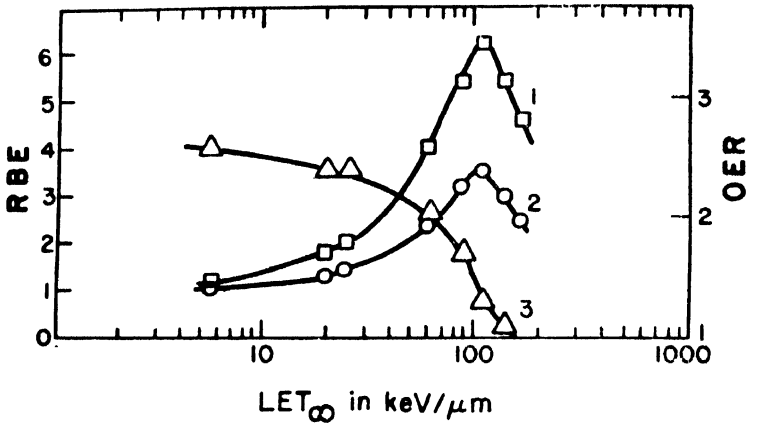

Figure 4. Variation of RBE and OER plotted as a function of LET (dE/dx).
1. RBE for cell killing at higher survival level.
2. RBE for cell killing at lower survival level.
3. OER.

Table I. RBE and OER of particles.

Radiation	RBE	OER
X	1	3
p	1.1	3
He	1.3	2.8
π^-	1.6	2.5
C	2	2.5
Ne	2.5	2
Ar	3	1.8
n	3	1.8

3.3. Fast neutrons therapy :

The first fast neutron therapy clinical trial was performed at Berkeley, California during December 1939-February 1943, a period long before the advent of mega-voltage radiotherapy and radiobiological techniques. Two hundred and twenty six patients with advanced tumors treated. After this trial, it was concluded "neutron therapy as administered by us had resulted in such bad late sequela in proporation to the few good results that it should not be continued". Reduction of the oxygen effect by fast neutrons was unknown at the time of these clinical studies. However, radiobiological experiments showed enhancement effect on tumors compared to normal tissues. In the light of radiobiological knowledge regarding the oxygen effect in radiotherapy and the reduction in OER for fast

neutrons, in Great Britain the need was felt to reinvestigate their use in radiotherapy. After a careful study of fast neutron effects on normal tissues and tumors, patient treatments were started at the Hammersmith Hospital, London, in 1967. After the initial encouraging results, a randomized clinical trial, to compare the clinical results of fast neutrons with megavoltage X or gamma rays, was started in 1971. Neutron treatments were given 3 days per week for four weeks. A total dose of 1560 rad of neutrons was given in 12 equal fractions. The tumor regression, relief of pain and ulceration after neutron treatment were found to be significantly better than photon treatments. The details of neutron therapy techniques are extensively discussed in a book by Catterell and Bewley (1979). These encouraging results from Hummersmith Hospital stimulated great interest around the world in the application of fast neutrons and other nuclear particles in radiotherapy.

A list of neutron therapy centers and the number of patients treated is presented in Table 2. Some of these centers are medically dedicated facilities with isocentric beam delivery capabilities to overcome some of the problems encountered with fixed

Table 2. Neutron therapy facilities.

Facilities	Country	Patients treated	Future facilities
~ 15	USA U K Netherlands (discontinued) Germany France Belgium Japan Korea Saudi Arabia South Africa India	~ 10,000	Super Conducting Cyclotrons (USA)

horizontal neutron beams. More than 10,000 patients have been treated with neutron beams in about 15 centers around the world. Fast neutrons appear to be the treatment of choice for inoperable salivary gland tumors. The other tumor types or sites for which neutron therapy may benefit are slowly growing, well differentiated soft tissue sarcomas, melanomas, and locally extended prostate adenocarcinomas. No definitive advantage for neutrons has been demonstrated so far in treating tumors of CNS, lung, pancreas bladder and cervix.

3.4. Proton therapy :

The potential application of protons and other heavy charged particles was proposed in 1946. The first clinical application of proton beams was conducted in Berkeley

in early 50's at the "184" cyclotron. Subsequently, the cyclotron was modified to further increase the energy making proton beams unsuitable for radiotherapy. However, the work was carried out using helium ion beams. Clinical work with protons has been ongoing in Sweden since 1956 and at Harvard since 1961, and in the Soviet Union since 1965. The Uppsala cyclotron is currently being modified and the patient treatments are expected soon. Most of the proton work in the USA was done using the Harvard Cyclotron. Radiobiologically, protons can be considered as a low LET radiation making it easier to apply the conventional radiotherapy experience to proton radiotherapy. Because of the Bragg peak effect and its sharply defined range, protons offer the potential to confine the high dose region precisely to the tumor volume and to minimize the dose to the surrounding normal tissue. The dose to the normal tissues outside the target volume was about 70% of the tumor dose using ^{60}Co gamma rays to about 22% using protons (see Figure 5).

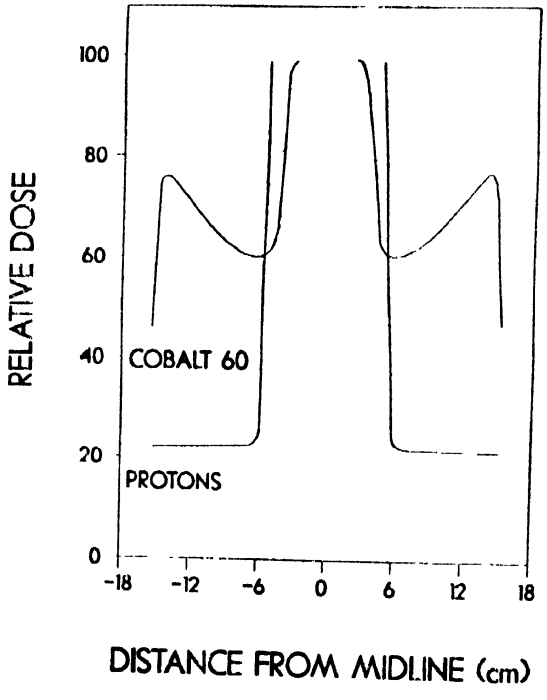

Figure 5. Dose distribution of protons compared to ^{60}Co gamma rays for two opposed fields.

In addition, the dose was more uniform throughout the target volume, including the edges. The use of a proton beam is almost like extending the skin sparing effect of megavoltage X-rays to all normal tissues in the beam path. Computerized tomography is being used for optimizing the treatment planning of proton beams. Table 3 shows the proton facilities in current use around the world.

The early work with protons was mainly confined to treating human diseases associated with the pituitary gland. Large field radiotherapy has been carried out

Table 3. Proton therapy facilities.

Number of facilities	Countries	Patients treated
Current (8)	USA Sweden USSR Switzerland Japan	~ 7000
Under Construction (9)		
Planned (5)		

in Uppsala since 1956 and in the Soviet Union in 1960's. The interest in fast neutron, pion and heavy ions (in radiotherapy) rejuvenated interest in protons and helium ions (since early 1970's) for large field radiotherapy using conventional fractionation. The ability to manipulate the dose in depth dimensions with heavy charged particles and the availibility of CT scanners helped develop three dimensional treatment planning techniques. These developments helped bring treatment volumes closer to target volumes which permitted the delivery of 10-30 % higher doses to the treatment volume without exceeding normal tissue tolerance.

Proton beams are the treatment of choice for choroidal melanoma for which the treatment earlier was mainly enucleation. Proton beams are also found to give impressive results for the treatment of chordoma and chondrosarcoma of the skull base and cervical spine (local control and disease free survival are 77 %).

With the routine use of CT scanners, the detection of arteriovenous malformations (A-V) has been increasing. The proton beams were found to be very effective in (A-V) treatment. This success accelerated the development in using narrow photon beams of megavoltage X-rays and gamma using multiple ^{60}Co gamma rays. The experience of helium ion beams is consistent with the proton beams.

The first medically dedicated proton accelerator is installed at Loma Linda University in California.

3.5. Heavy ions :

Two accelerators, a low energy heavy ion linear accelerator and a high energy proton accelerator, (Bevatron), located nearby at Lawrence Berkeley Laboratory, were connected with a beam line in 1974. With some modifications in both accelerators, heavy ions such as C, Ne and Ar were accelerated with adequate intensity and range for radiotherapeutic application. This combined facility is known as BEVALAC. It is interesting to note that the radiotherapy interest of

heavy ions helped get the heavy ion physics research started. Heavy ion facilities are currently being built in Germany and Japan.

The dose localization characteristics of heavy ions are similar but slightly inferior to proton and helium ions. The LET of these beams, especially in the peak region, is much higher and increases from the proximal to the distal region of the modified Bragg peak. Since these changes in LET introduce changes in RBE across the treatment area, the dose across the peak is varied to produce uniform biological effect. The techniques of shaping dose distributions to get uniform biological effect were developed for various heavy ions such as C, Ne and Ar and clinically relevant RBE values were determined. The tumors that are found to respond well for fast neutrons can, in principle, be treated better with heavy ions because of their good dose localization characteristics. About 300 patients were treated with heavy ions which led to randomized trials for lung, prostate, salivary gland, nasopharynx, soft tissue sarcoma and glioblastoma tumor sites.

3.6. Negative pions :

Application of pion beams for radiotherapy were proposed in 1961. Pion beams of intensities suitable for radiotherapy became available only in the 1970's.

Three pion beam facilities built mainly for physics research, but with adequate facilities for therapy, are located at Los Alamos, USA, Vancouver, Canada, and Villigen, Switzerland. The Swiss facility incorporates a pion collection device developed at Stanford University. This device permits simultaneous multiport irradiation of the tumor volume.

A total of nearly 1000 patients have been treated among the three facilities and the optimal doses for treating patients were developed. The program in Los Alamos was discontinued in the early 80's, but the programs in Canada and Switzerland are active. The Canadian group reported encouraging results in treating glioblastoma using a randomized trial. The Swiss group reported encouraging results in treating non-resectable soft tissue sarcomas.

4. Conclusion

Particle therapy programs gave an impetus for further developments in radiation physics as well as in radiation biology. These programs also helped to attract many talented high energy physicists that contributed developments of three dimensional treatment planning which, in turn, is helping to improve conventional radiotherapy. Particle therapy also is paving the way towards individualized radiotherapy treatments. The impact of particle therapy, so far, has been in the treatment of relatively rare tumors.

Methods should be developed to identify tumors that have a better prognosis for high LET, perhaps from a biopsy taken before treatment. The pitfall of the particle radiotherapy, in general, has been that the expectations were too high and

it is quite possible that further improvements in radiotherapy may become apparent in less spectacular ways. Finding optimum doses of high-LET particles that need to be used to be minimize recurrences and still be within acceptable tolerance limits of normal tissues turned out to be more complicated than expected.

A well-coordinated, international effort is needed to assess the potential for heavy particles in therapy. Such an effort between Europe and the USA is in progress and the extension of this coordination to other countries is being sought since it takes a large patient pool to conduct various therapeutic trials.

Evaluation of a new method and the presentation of convincing clinical evidence requires ten years or longer ; hence progress is very slow and comes in small steps.

The use of nuclear particles in cancer treatment provides an excellent opportunity for interdisciplinary research involving physicists, engineers and biomedical scientists to develop new techniques for tumor diagnosis, localization, and treatment planning.

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